Journal of Engg. Research Vol.10 No. (2B) pp. 248-263 DOI: 10.36909/jer.11297

Bone remodeling model integrating the biological function and damage influences for the cortical-trabecular interface

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Submitted *:* 08/08/2020
Revised *:* 02/07/2021
Accepted *:* 15/07/2021

ABSTRACT

Bone remodeling process has been widely investigated in literature from an experimental and theoretical viewpoint. Indeed, the biological process of bone remodeling allows a continuous renewal of the microstructure over time, and thus it contributes in decreasing the bone damage by repairing it. This research work aims to study the biological function's (f_{bio}) effects on the bone remodeling process trough bone density evolution. Parameter f_{bio} is one of the important parameters that controls bone volume variation. The biological bone remodeling process is modeled in terms of equations describing the activity of the Basic Multi-cellular Units (BMU). We use a mathematical model to simulate damage repair, based on Garcia Aznar's model. The results of simulation show a good match with experimental and clinical data: bone porosity decreases over time and decreases also as the biological factors increase. In the same view, the apparent density (ρ_a) decreases when bone volume fraction increases. We note that the governance of the evolution of bone density leads us to consider the evolution of bone volume during youthful and the maturation phase with their saturation zone for adult in terms of growth.

Keywords: Bone remodeling process; Bone volume fraction; Stimulus; Damage; Biological function.

INTRODUCTION

The subject of bone regeneration was constantly a large research domain for study by specialists. The complexity of human bone tissue and its micro architecture continuous changes are making this subject one of the most interesting research topics. Bone evolution can be described through a process called bone remodeling that allows the bone regeneration. Before birth, the bone starts to form, and then the bone remodeling process keeps renewing bone throughout life, to repair the occurring micro-cracks. This mechanism managed by the bone remolding unit (BMU) mainly composed by osteocytes, osteoblasts, and osteoclasts bone cells. The bone cracks can be restored by the succession of resorptions and formations cycles ensured by bone cells actions. Several factors are influencing bone development such as biological factors, endocrine factors, physical activity, diseases,

genetic factors, race, and gender (Barkaoui et al., 2017; Ben Kahla et al., 2018; Ait oumghar et al, 2020; Ben Kahla et al., 2021).The human bone development study remains a vast subject of research because of the lack of experimental data results. The full regulatory mechanisms of (BMUs) are not yet established, which makes the formulation of several cellular models more complex. Numerous mathematical models representing bone remodeling can be found in literature. The first studies were done by Frost (Frost, 1969) and Martin (R. Bruce Martin et al.,1972). They described the BMU and the osteoblasts and osteoclasts behavior, partly. They described the idea of cell activation and showed that the mechanical stimulus and the damage accumulation affect the initiation of cells activity. A mathematical model of bone remodeling was developed that takes into account the complete activity of BMUs considering the bone mineralization degree, but it does not take into account the modeling of cell population was developed by (Komarova et al.,2003; Pivonka et al., 2008; Barkaoui et al., 2019). In 2001, a model which includes the notion of BMU activation function in order to describe the bone remodeling process was proposed by (Garcia et al., 2005).It has been proved that the BMU's are always migrating to the region of damaged bone before the start of bone remodeling process. Hence, osteoclasts follow the stress direction. The first mathematical model of bone remodeling describing the dynamic behavior of bone cells at a single BMU was established by Komarova et al., 2003, which includes autocrine and paracrine factors in addition to Paget's disease. This model studies these parameters' effects on bone mass behavior. Then, a mathematical model was developed, focusing on several biological factors influencing bone cells activation and repression by (Nazarian et al., 2008). This model was extended by Pivonka et al., 2008, who added a rate equation of Bone Volume (BV) and described the expression of the main biological factors contributing to bone remodeling process (the receptor activator of nuclear factor NF-kB-ligand (RANKL) and the receptor osteoprotegerin (OPG) that were neglected before). Unlike the other studies, this study considers the materials properties evolution and the biological information delivered by the osteocytes. This information is captured by the activity of the osteocyte which will modulate the inhibition of BMU activity. All this improvement for the mathematical models still needed further developments. Indeed, to investigate some bone diseases types such as osteoporosis, it is important to take into consideration several parameters. For example, bone mass and porosity assessment in elderly population depends on their values in childhood; which in their turn depend on bone microarchitecture in this period. Thus, bone microarchitecture associated age is an important parameter in bone renewing, as the bone remodeling occurrence depends on the available bone surface. It has been proved by several scientists that there is a particular bone compartment to be underscored, which is the intermediate zone. This part is located between the cortical and the trabecular bone and characterized by a gradually varying density from the cortical to trabecular bone (Adams et al., 2018; Martin,1984). According to Zebaze et al.,2013, considering this bone part could make the estimation of fracture risk and aging effect more accurate. The pathophysiology of osteoporosis affects the trabecular structure but not the mineralization of bone tissue. As a result, changes in the trabecular structure due to unbalanced bone remodeling affect the mechanical stability of the cancellous network, which is disproportionate to the change in mass. The pathophysiology of osteoporosis affects the trabecular structure, but not the mineralization of bone tissue. Therefore, variations in trabecular cross-sectional area related to rebalancing of bone remodeling affect the mechanical stability of the cancellous network, which is disproportionate to the fluctuation in mass. The bone volume fraction of cancerous bone was 33% lower than normal bone (Nazarian et al., 2008) and was not different from that of osteoporotic bone (Parfitt et al., 1987; Laurent et al., 2002; Ghislain et al.,2014; Khaled , 2021; Khaled et al., 2015; and Khaled et al 2015). In our research work, we propose to investigate the relationship between bone remodeling process and the biological function f-bio in the intermediate zone for children aged 9 years old and 19 years old. Based on Berli et al., 2017; Garcia et al., 2005, works, we have implemented a resorption/formation cycle taking into consideration the mechanical and biological factors, affecting the bone remodeling process. Then, by acting on the bone density, we computed the bone volume fraction (BVF) over time and for different f_{bio} values. In bone tissue histology, areas of thinner bone are typically regarded as more youthful bone, indicating that areas of intermediate porosity, which include bone of a lesser bulk density, do so because they exhibit a higher level of remodeling. The work done by Berli et al. and Adams et al. described this phenomenon as a mechanism known as a surface-moderated effect, where the higher the available specific surface area is, the greater the rate of

remodeling and the lesser the material density, because of increased osteoid generation and occurrence. Garcia et al., 2005 suggest a model that describes the biological bone remodeling process modeled in terms of an equation that describes the activity of BMUs. Nevertheless, by experimental methods of Archimedes and by CT scan, Adams et al., 2018; Adams et al., 2014; Berli et al., 2017; and Zioupos et al., 2008, discuss the presence of intermediate region in the bone tissue. This model considers that osteoclasts primarily resorb the parts of the bone closest to the surface, which are younger and less mineralized than the older inner parts. In this work, we combined the sets of works to describe the evolution of the different parameters for two defining ages, 9 years and 19 years.

BONE REMODELING APPROACH

Bone strength is related to bone density and its microarchitecture, while the morphological characteristics of bone depend on its size and its porosity. Bone, as we know, is a living material, where the remodeling process is the only way to get renewed over time and throughout life. It is composed of a strong and compact external layer, called cortical bone, assembled with a less dense branched network of bone matrix, called trabecular bone. It has been observed that cortical bone is getting trabeculated near the endostyle due to the proximity of the Haversian pores (Thomas et al., 2005).This observation pushed many researchers to think about the identification of a new bone section separating the compact and the spongy bone. This compartment joining two types of bone has been named the transient, the intermediate, or the intra cortical/ trabecular zone (see Figure 1).

The internal bone structure is characterized by a variable porosity and density, which makes the bone mechanical behavior change from a zone to another. Being classic zones, the cortical and trabecular zones have been well investigated in many previous studies (Garcia et al., 2005; (Hernandez et al., 2000; Komarova et al., 2003; Khaled , 2021 and Khaled et al.,2015; Khaled et al 2015). However, very few studies have been devoted to the exploration of the intermediate zone, especially during growth. In this work, we are interested in this bone part and the specific surface area since the remodeling process occurs in external bone surface. The specific bone surface is related to the inclination of the tissue to be reestablished (Lerebours et al., 2015). This area depicts the thickness of the surfaces on which osteoclasts and osteoblasts are acting. It likewise characterizes the regions through which the biochemical signals are sent to bone cells by osteocytes; these signals are the result of the osteocytes transduction capacity which expresses the mechanical loads impact on bone by biological factors (Marotti, 2000). The remodeling process is activated by a mechanical stimulus that depends on external loads and the bone mechanical characteristics. These factors are also relying on the mineralization of studied zone (Martínez-Reina et al., 2008; Garcia et al., 2005). Besides all the characteristics, in our model, the mechanical setting including the state of degradation was also considered.

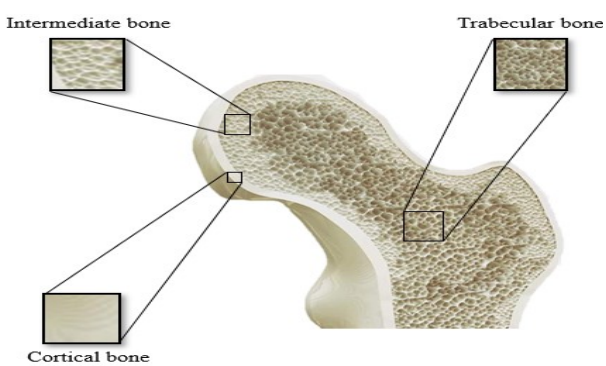

Figure 1. Femoral head mainly composed of trabecular bone, covered with a cortical bone shell and an intermediate bone.

We present the internal factors that describe bone tissue as an auxiliary material. The evolution of these factors is governed by diverse mechanical and biological factors that we show as a function of time. In our model, (*tr*) is the resorption period, which represents the period when the BMU acts due to the movement of osteoclasts. This period is followed by an inversion time (*ti*), afterwards, in which bone statement is carried out by the osteoblasts throughout the formation time (*tf*). Based on Frost's study (Frost, 1969), we will concentrate on the period during which the active osteoclasts are dynamic. Relying on this condition, it is going to be easier to define the longest surface travelled by a BMU using its rate of progression, called BMU rate, and its lifetime noted ($v_b(t) = \int_{t\max m}^{t} \frac{\dot{v_b}(\tau)}{d\tau} d\tau$). Bone fixation requires both the expulsion of harmed tissue and a drawn-out regenerative one to accomplish an anatomical and practical reclamation of bone. Macrophages are likewise a key mediator in bone injury recuperating and crack fixing, as they are involved in various phases of the fixing procedure. To perform the various functions of bone formation/resorption and repair, cells are taking special forms which change according to their morphological function and characteristic location. The change in the bone volume (BV) over time can be estimated using a formula that describes the rate of total BV (Pivonka et al., 2008). It is expressed as follows:

$$\frac{dB_V}{dt} = AF(-v_r + v_f) \tag{1a}$$

Where

- B_v denotes the total volume;
- AF is the activation frequency of the BMU which corresponds to the total amount of BMUs involved by unit of time. One day is chosen as a time step to reduce the simulations time and complexity;
- v_r and v_f are, respectively, the capacity of the resorption crack and the volume formed per unit of time by all BMUs active at time t.

The volume fraction of bone material makes the bone differential created on day τ and still present at time t. It is

$$v_b(t) = \int_{t\max m}^{t} \frac{\dot{v_b}(\tau)}{d\tau} d\tau \tag{1b}$$

where $t_{m\max}$ is the time required for part of the bone material to reach the maximum level of mineralization.

Over time, some parts of the bone are formed building the (v_f), while others are resorbed to create the (v_r). At each time step, (v_f) and (v_r) update the substantial BV. Therefore, the proportion of change in the BVF has to be subjected to the volume resorbed and formed by all the active BMUs at each time (t) (Martínez-Reina et al., 2008; Berli et al., 2017). It is expressed by

$$\dot{v_b} = \dot{v_f} - \dot{v_r} \tag{2}$$

Bone volume fraction (BV/TV) is the volume of mineralized bone per unit volume of the sample. These changes in the BVF are linked to the active density functions that will be represent by $N_{BMU}(BMU_s / mm^3)$.

After activation, a BMU moves through a distance defined by $L_{BMU} = \sigma_L v_{BMU}$ where σ_L is the BMU_s lifespan and v_{BMU} is its rate. Each portion influencing the progression of BVF could be defined by

$$\dot{v}_{BMU}(t) = \int_0^{L_{BMU}} \left(\int_{t'-\sigma_L}^{t'} \dot{N}_{BMU}(t'')dt'' \right) \dot{A}(x)dx \tag{3}$$

where

- $\dot{N}_{BMU}$ is the BMU activation frequency,
- dx is restrained by the route of BMU's development, and
- $\int \dot{A}(x)dx$ is the rate of volume variation per length unit in a specific point x along the progression path.
- $\int_{t'-\sigma_L}^{t'} \dot{N}_{BMU}(t'')dt''$ controls the number of active BMU at the time (t').

We suppose that the remodeling rate in the transversal direction is perpendicular to the movement direction (Garcia et al., 2005). In case of resorption and formation, the remodeling rate will be expressed by

$$\dot{A}(x)dx = \begin{vmatrix} \frac{A_{BMU}}{t_r} f_c \\ \frac{A_{BMU}}{t_f} f_b \end{vmatrix} \quad (4) \tag{4}$$

where

- f_b and f_c are normalized variables defining the activity of osteoblast cells and osteoclast cells, respectively.
- A_{BMU} is the whole cross-sectional zone of a BMU.

dx will be articulated relatively to the proportion of a BMU movement by $dx = v_{BMU}dt$.

By combining Equations (2) and (3), the BV resorbed and formed will be expressed as follows:

$$\dot{v}_f(t) = \int_{t-t_r-t_i}^{t-t_r-t_i} \left(\int_{t'-\sigma_L}^{t'} \dot{N}_{BMU}(t'')dt'' \right) \frac{A_{BMU}}{t_f} f_b(t')v_{BMU}dt' \tag{5a}$$

$$\dot{v}_r(t) = \int_{t}^{t-t_r} \left(\int_{t'-\sigma_L}^{t'} \dot{N}_{BMU}(t'')dt'' \right) \frac{A_{BMU}}{t_r} f_c(t')v_{BMU}dt' \tag{5b}$$

Equation (5) describes BVF evolution as a function of time (t) via the evolution of BMU density. With every time increment, $v(t)$ have to be updated considering the amount of bone material formed $dv_f(t) = v_f(t)dt$ and resorbed $dv_r(t) = v_r(t)dt$.

The factor (f_{bb}), known as the focal bone balance (Hernandez et al., 2000; Keller et al., 2001) controlling the formed and resorbed bone amount during remodeling, is expressed by

$$f_{bb} = \frac{f_b}{f_c} \tag{6}$$

This equilibrium is strongly connected to the mechanical stimulus (Doblar et al., 2002; Carter et al., 2003). The mechanical stimulus has been identified as a daily bone deformation in the form of a scalar quantity to introduce several load cases (Whale et al., 1986). In addition, the mechanical effect is defined by a scalar magnitude according to the idea proposed by (Mikic et al., 1995), representing the deformation per day that depends on the charge cycle. The following form presents the mechanical stimulus:

$$\xi = (\sum_i N_i \varepsilon_i^{-m})^{\frac{1}{m}} \text{ (7).}$$

- M is a parameter taken equal to 4.
- N_i is the number of cycles.
- ε_i is the strain resulted from each load case i.
- In the literature, the effect of f_{bb} is not taken into account in cortical bone formation because of the insufficient space for bone filling; that is f_{bb}=1. Trabecular bone is the site which is more likely to be renewed in our case (people aged less than 65 years old). Therefore, it is going to be the less dense part of the intermediate bone. The life expectancy of osteoclasts and osteoblasts is shorter than the BMUs one. Thus they should be continuously reconstructed during the produced BMU's progression.

The quantity of dynamic BMUs is constrained by their lifespan σ_L and the frequency of their stimulation. Fluctuations in the quantity of formerly active BMUs could result from any overrun of their lifetime, a decline in their quantity, or the creation of new BMUs. The number of BMUs per unit of time is expressed by (Martínez-Reina et al., 2008)

$$\dot{N}_{BMU} = f_{bio}(1-s)S_v \tag{8}$$

where

- s is the mechanical signal received by the osteocyte and
- S_v is the available tissue surfaces.

Bone tissue continuously remodeled through actions of bone cells, which include bone resorption by osteoclasts and bone formation by osteoblasts, whereas osteocytes act as mechanic-sensors and orchestrators of the bone remodeling process. This process is under the control of local (e.g., growth factors and cytokines) and systemic (e.g., calcitonin and estrogens) factors that all together contribute for bone homeostasis. For instance, the

coupling from bone resorption to bone formation is achieved by interaction between osteoclasts and osteoblasts. Moreover, osteocytes produce factors that influence osteoblast and osteoclast activities, whereas osteocyte apoptosis is followed by osteoclastic bone resorption. This signal (s) is sensitive to any disturbance that causes an activation; this disturbance could be a result of a low level of deformation, or of the presence of microcracks that disrupt cellular connectivity. Thus, (s) inhibition s depends on the level of the damage (d) and the mechanical stimulus (ξ) which is expressed by (Garcia et al., 2005)

$$s(\xi,d)=\frac{\xi}{\xi+c}(1-d)^{a} \tag{9}$$

where c and a are the prototypical constraints that define the transduction character of the mechanical stimulus $\xi$and the damage d. The choice of these parameters was our task, aiming to find accurate results in concordance with many experimental data. Concerning the available tissue surface (S_v), it has been found in the literature that there is a remarkable phenomenological relationship between it and vascular porosity (f_{vas}). According to R Bruce Martin ,1972, it is expressed as follows:

$$S_v = af_{vas} + bf_{vas}{}^2 + cf_{vas}{}^3 + df_{vas}{}^4 + ef_{vas}{}^5 \tag{10}$$

S_v is a key parameter characterizing the trabecular architecture and the surface-to-volume ratio(S_{vr}). Many authors have studied S_v, and they supposed that it is equal to S_{vr} in the case of a perfect microstructure model. Moreover, they have shown a close relationship between S_v and the density fraction or volume fraction (Parfitt et al., 1987). According to their work, S_v can be written depending on bone density (ρ) as follows:

$$S_v = -0,2412 + 24,8\rho - 64,7\rho^2 + 103,7\rho^3 - 67,5\rho^4 \tag{11}$$

The other morphological parameter of S_v is porosity, and it is expressed as a function of bone mass portion as follows (S et al. 2001):

$$p = 1 - v_b \tag{12}$$

v_b (BVF) corresponds to the ratio between the bone volume (BV) and the total volume (TV) as follows:

$$v_b = \frac{BV}{TV} \tag{13}$$

Our proposed model is built following similar steps to those presented by Garcia et al.,2005; Berli et al., 2017; and Martínez-Reina et al., 2008. The model consolidates a remodeling process where osteoclasts and osteoblasts are acting on the same surface. This model is based on the hypothesis that osteoclasts will only resorb the newly formed bone matrix which is closer to the surface, and thus the mineralized bone matrix localized in the depth will not be considered. Bone equilibrium is defined when the amount of resorbed bone is equal to the amount of formed bone analyzed using the previously obtained Equation 2. In order to represent the cellular mechanism in the bone remodeling process, we proposed an approach considering the cellular interactions initiated by a stimulus where

density (ρ_n) can change according to time steps (n) for each interaction point presented in Equation 14. Based on this formula, the remodeling rate and surface density (Sρ) can be evaluated for each ρ:

$$\rho_{n+1}(t) = \rho_n(t) + n(t) \quad (14).$$

Besides, this calculation of density will allow us to determine the new BVF. However, the estimation of the bone volume fraction's range, in our case, could be limited by the characteristics of the studied zone, which is the transient zone. According to Berli etal., 2017, the BVF considered in the intermediate zone should be between 0.3 and 0.7. On the other hand, we supposed that osteocytes are the responsible actor of remodeling damaged areas' initiation, as previously reported by Raggatt et al., 2010. We have brought together all the ideas described above in our proposed bone remodeling algorithm (see Figure 2).

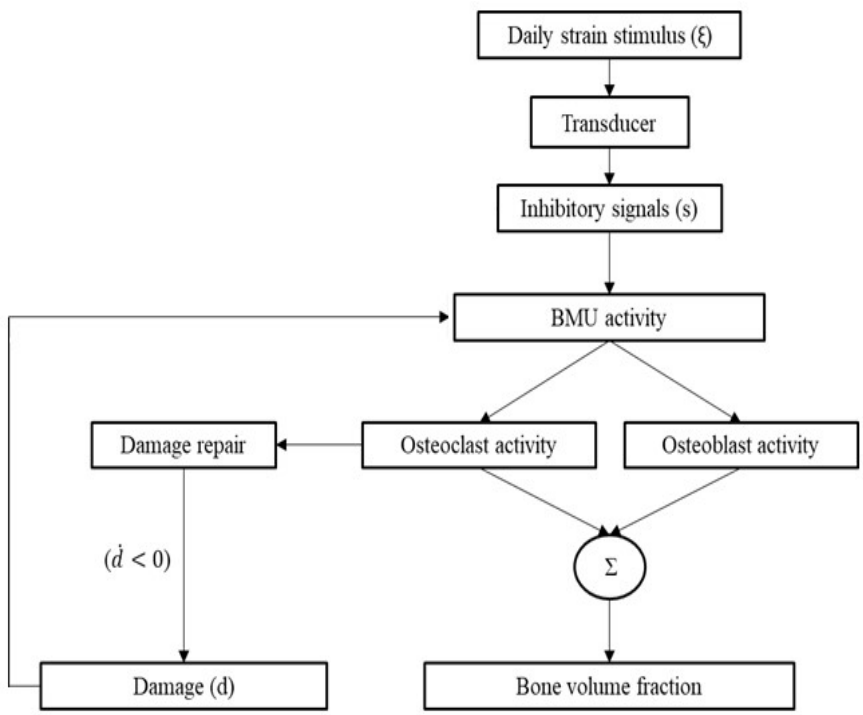

Figure 2. Schematic representation of the proposed BR algorithm.

This algorithm does not include the mechanical damage, but it considers the compensation for damage. The implementation of the transduction model highlights the mechanical and biological factors necessary for bone adaptation. This approach allows the simulation of local bone remodeling in the intermediate zone (see Table 1). A combination of Equations 2, 5a, and 5b presents the strategy for defining the BVF. All equations from the bone remodeling approach (Garcia et al., 2005; Pivonka et al., 2008) were used in our modeling.

RESULTS AND DISCUSSION

In our work, we have fixed the porosity range [0.3 ± 0.6] (Berli et al., 2017) as a first step. The intermediate bone was subject to various mechanical stresses that can lead to damage the bone. In response to these mechanical

stimulus, the biological process of bone remodeling is initiated, and the observed changes in the mechanical and morphological properties are intendedto enhance bone resistance against the external loading. Two types of biological markers are involved in the boneremodeling process: the firsts are markers associated with formation and the seconds are markers associated with resorption. Biological factors, which areimplanted inour model as fbio, are the determining factor for the presence and development of theintermediate zone and all the bone parts. The results showed that fbio could represent differentlevels of formation or resorption that influence the evolution of BVF, porosity and ρa duringtime. The Fig. 3shows the effect of fbio on the BVF over time at the BMU level, for differentfbio levels ranging from a minimum value of 0,001 to 0,03.

Table 1. Values assimilated to the different model parameters.

Parameter		**Range**
General parameters		
Number of daily charging cycles	Ni	10.000 (García-Aznar, Rueberg, and Doblare 2005) 3285-8395
Load Exponent	m	4 (Whalen, Carter, and Steele 1988)
Minimum focal balance	f_{bbmin}	0,5-0,8.
Stimulus activation curve parameter	c	0,0025
Damage activation exponent	a	40
Frequency of biological activity	f_{bio}	0,001-0,012-0,013-0,015-0,5-0,01-0,02-0,025-0,03
Initial damage	d_o	0 (García-Aznar, Rueberg, and Doblare 2005)
Initial equilibrium stimulus	ξ_0^*	0.0025 (García-Aznar, Rueberg, and Doblare 2005)
Characteristic parameters of the BMUs activated and geometry		
Resorption period	tr	60 days (García-Aznar et al., 2005)
Reversal period	ti	56 days (García-Aznar et al., 2005)
Formation period	tf	175 days (García-Aznar et al., 2005)
BMU lifespan	σ_L	100 days (García-Aznar et al., 2005) (Berli et al.,2017)
Osteonal diameter	d_0	0,075mm (García-Aznar et al., 2005)
Haverse diameter	d_h	0,0145mm(García-Aznar et al., 2005)
Osteon depth	d_e	0,0491mm(García-Aznar et al., 2005)
BMU width	d_{BMU}	0,152mm (García-Aznar et al., 2005)
BMU width	v_{BMU}	0,01/day (García-Aznar et al., 2005)
Time to reach the maximum mineral level	$t_{m\max}$	4000days (Berli et al. 2017)

A high value of f_{bio} leads to an oscillatory behavior of the bone response. The BVF increasesand reaches its maximum at the age of 9 years. We can observe the evolution of the BVF for many f_{bio} values, then we note that when f_{bio} increases, the BVF rises also progressively. It can be seen that at the age of 6 years (2190 days) a strong increase for bone volume until the age of 9 years (3285 days). In Figs.4 and 5 an increase in bone resorption as well as bone formation canbe observed depending on the biological function's increase. However, this increase is onlyrestricted on the period between the (2750th) and the (3000th) days in the formation case.Thus, the effect of the factor (f_{bio}) shown in equation 6 is verified. Knowing that we considered that (f_{bb}<1), we had more resorption than formation as a result.

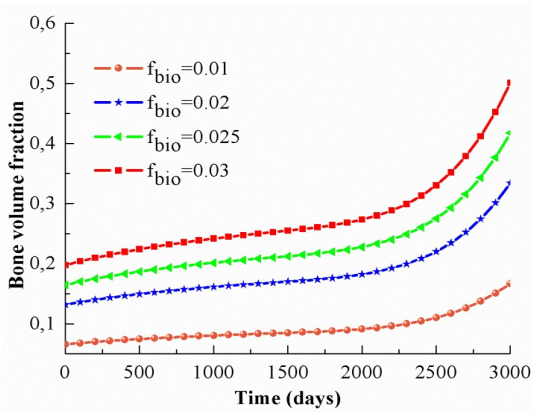

Figure 3. BVF evolution over time for biological function values (0.01-0.02-0.025-0.03) (for 9 years).

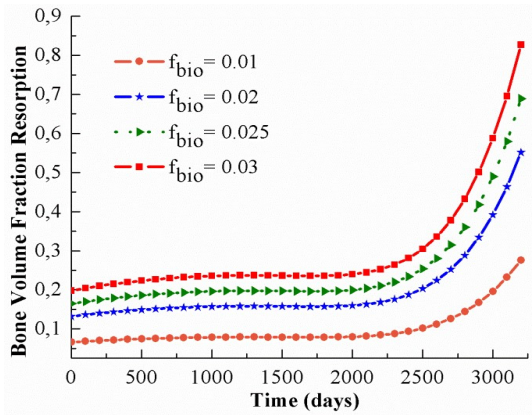

Figure 4. Evolution of the BVF resorption as a function of biological functions (0.01-0.02-0.025-0.03).

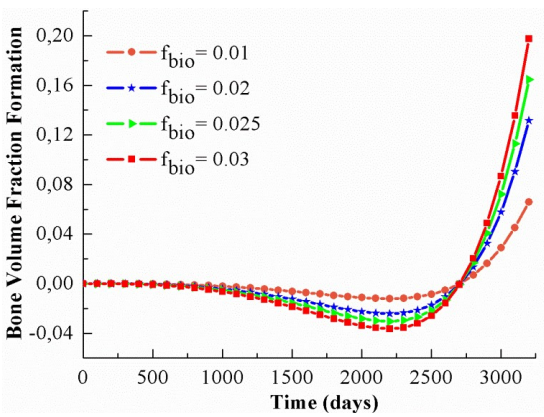

Figure 5. Evolution of the BVF formed as a function of time in the case of equilibrium for biological function values (0.01-0.02-0.025-0.03) (for 9 years).

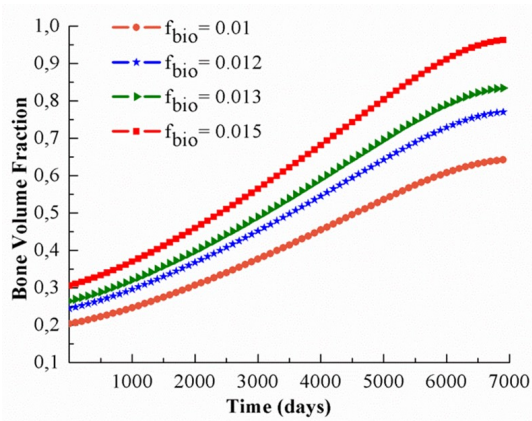

Figure 6. BVF evolution over time for biological function values (0.01-0.02-0.025-0.03) for 19 years.

From the age of 9 to the age of 19 years, the BVF continues to increase (see figure 6 and 5) and reaches its peak at the age of 18 years; after that, BVF is gradually decreased.

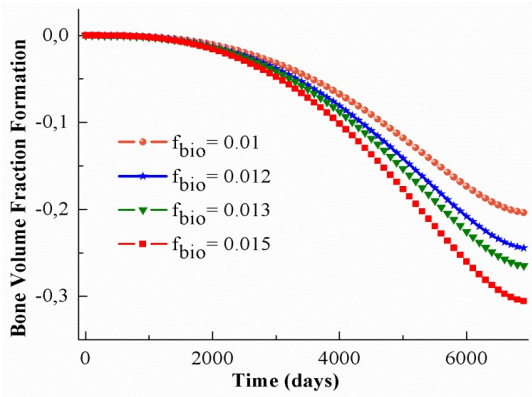

Figure 7. Evolution of the BVF formed as a function of time for biological function values (0.01-0.02-0.025-0.03) (for 19 years).

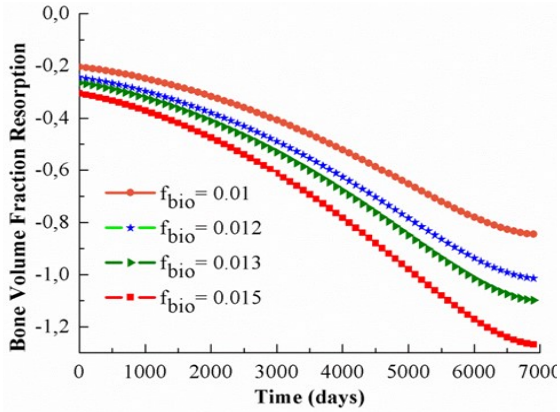

Figure 8. Evolution of the BVF resorption as a function of time for biological function values (0.01-0.02-0.025-0.03) (for 19 years).

In Figures 7 and 8, we present the evolution of BVF as a function of time for different values of f_{bio} in case of formation and resorption. The evolution of the BVF continued during the age of 19 years with the same amplitude but, negatively assuring the balance between the resorbed and formed amounts (see Figures 7 and 8). Indeed, on the surface, the BVF maintains the same value over time even the bone formation decreases because, in our case, we are dealing with a healthy bone to analyze utilizing the previously obtained equation 2. In Figures 9 and 10, we present the progression of porosity as a function of time. The porosity decreases over time, and almost at the age of 18 years, the porosity stabilizes at 0.23 for a value of f_{bio}=0.012 BMUs/mm^2/day.

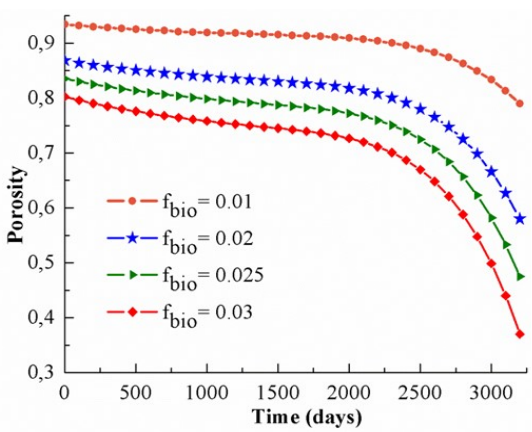

Figure 9. Evolution of porosity over time for biological function values (0.01-0.02-0.025-0.03) (for 9 years).

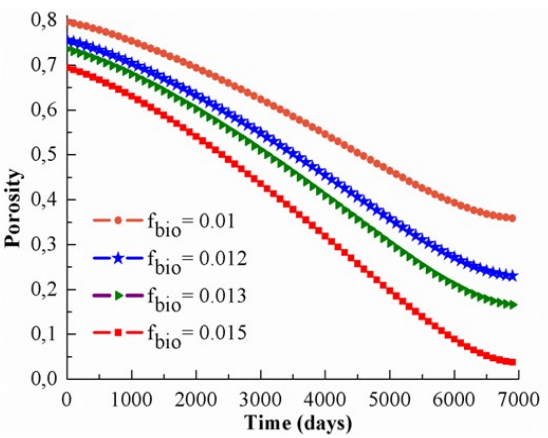

Figure 10. Evolution of porosity over time for biological function values (0.01-0.02-0.025-0.03) (for 19 years).

Hence, to show the relationship between the BVF and ρ_a to evaluate the effect of f_{bio} on them, we proposed the Figures 11 and 12. In these figures, we have found that the maximum value of ρ_a in the age of 9 years reaches 1.44 g/cm2. This density value is higher than the value detected at the age of 19 years, which is 0.96 g/cm2.

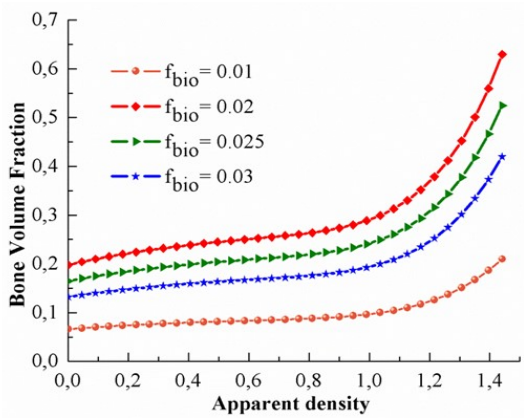

Figure 11. Evolution of the BVF as a function of bulk density for different values of biological function (9 years).

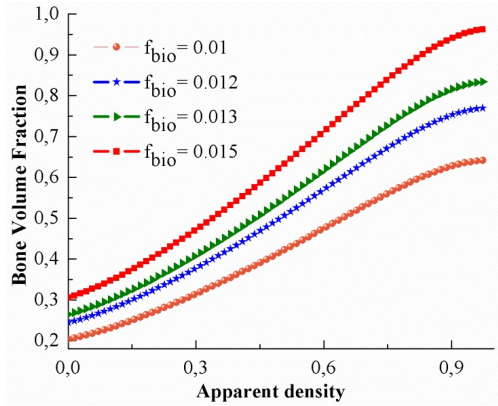

Figure 12. Evolution of the BVF as a function of bulk density for different values of biological function (19 years).

According to experimental results (Amidzic et al.,2008),it has been explained that the BVF decreases in the absence of stress, then, it has been optional that micro damage triggered by exhaustion or by the overload could activate the bone remodeling process in the purpose of repairing the damaged areas. We propose to use the inhibition theory proposed by (R. B. Martin,2000) where it is assumed that the osteoblasts cells that form bone are triggered to activate BMU activity receiving an osteocyte network inhibitory signal. At a low stress level of damage, the inhibitory signal affects the evolution of the BVF.Fig.13 show a normalized level of signal as a function of low stress stimulus and damage state as it is expressed in equation 9, with c=0.0025.

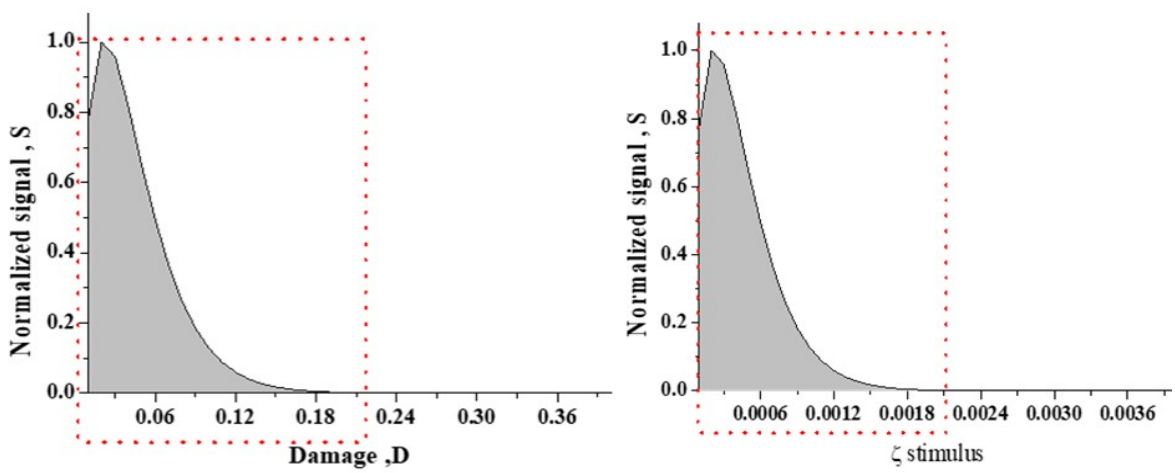

Figure 13. Normalized level of signal as a function of low stress stimulus and damage state expressed in Equation (9) with c=0.0025.

As well known, the biological process of bone remodeling allows the continuous renewal of the microstructure over time and thus, contributes to decrease the bone damage by repairing it and limiting its expansion. The present work aims to refine the study of the biological function (f_{bio}) effect on the bone remodeling process by acting on the bone density evolution. Concerning Figures 4 and 5 results, we assume that the maximum value of the BVF reached by the remodeling cycle of a BMU is equal to 0.41. This choice could be validated by the work of (Berli et

al.,2017). They noted that if the BVF is less than 0.7 (v_b>0.7), we describe the cortical part then, if it is less than 0.3 (v_b<0.3), we describe the trabecular part. Besides, as mentioned before, the transition zone is defined when 0.3< v_b <0.7. This evolution is the result of the transformation caused by the osteoclast cells that are responsible of bone resorption (Fig. 4) and the osteoblasts ones that are responsible of formation (Fig. 5). The increase of resorbed BVF during the BMU activity represents an anomaly in the bone remodeling cycle, which may be related to a brief period of sex hormone deficiency. In addition, it could be linked to the distance between opposite hemi-osteon lines in trabecular bone. Otherwise, the decrease of resorbed volume is due to stresses that may occur throughout life. There is a decrease in pore thickness, if the depth of resorption increases with age. This decrease in porosity reaches the intermediate part progressively over time. We believe that this diminution is linked to a reduction in stem cells in the osteoid cells' line and to the diminution of their lifetime. In addition, it is important to say that (Pennline and Mulugeta 2017) discussed relationship between bone mineral density and BVF ,which could relate our results to the experimental data. Considering the evolution of the BVF over time associated to different value of f_{bio}(see Figure 6),we found that our results are approximately matching with the experimental results, which have shown that bone mineral density predicts the stabilization zone (Kalkwarf et al.,2007). After many observations we have found that bone mineral density and BVF have approximately the same evolution behavior (Pennlineet al.,2017). Additionally, the results presented in Figures 7 and 8 could be explained by: for each BMU, bone formation and resorption are firmly connected in the delicate bone parties to keep up the balance in terms of bone mass. With maturation, the BMU values evolves in a negative way approving that in this period, there is an increase of bone resorption and a decrease of bone formation. The growth of bone differs from a child to an adult. Indeed, during childhood the minimum rate of development is observed around the age of 2 to 3 years. After that, the speed of bone formation increases progressively in the age of 5 to 6 years. Thus, the BVF curve is characterized a rapid increase in the first six years and its maximum value is detected at the age of nine years old. This period is followed by the teen-age period, which is characterized by an acceleration of bone structure growth. After this peak, the speed of growth decreases rapidly to stabilize at the age of 18-19 years. The saturation zone, in this period, was mentioned in the literature (Cole,2012).We note that the increase in the rate of f_{bio} decreases the porosity; then the decrease of porosity fluctuates the global structure of bone, which make it have a tendency to a cortical structure. That is observed in such evolution of porosity in Figures 9 and 10. Besides, the decrease in Figures 11 and 12 could be explained by the change in the BVF state resorbed and formed within the BMU. We can see that f_{bio} influences the BVF, but it has no significant effect on ρ_a. This findings matches with (Pennline et al.,2017)'s work. We have shown before that the frequency of f_{bio} origin is an important parameter in controlling the BV variation (recall equation8), as a high f_{bio} value leads to increase bone response (Garcia et al.,2005). Based on the results previously shown and the literature, we think that the perfect $f_{bio}$to be taken is f_{bio}= 0.02 BMUs/mm2/day for the age of 9 years and f_{bio}= 0.012 BMUs/mm2/day for the age of 19 years.

CONCLUSION

This work provides a formulation of bone formation and bone resorption located in the bone intermediate zone. The study presents an analytical approach to surpass complications related to study experimentally. The algorithm of remodeling defines and offers some hypotheses to find an appropriate mathematical model for bone evolution. We have tried to show that bone volume is increasing trough bone surface over time and that the BVF has the same evolution of apparent density over time as well. We have shown the reaction of the studied area to the biological factors. Besides, the degradation of bone mechanical properties due to various mechanical loads makes the comprehension of the coupling between the collection of damage caused mechanically and natural bone reactions difficult. The studied model could be applied to detect connection between the elements of remodeling and the organic factors involved to determine the minerals circulation within the bone. Their movement connected to the accessible surface for remodeling and the porosity of the concerned zone. On the other hand, age impacts the mechanic-transduction capacity of osteocytes and the quality of the remodeling process. In our model, we considerate this osteocytes characteristic by integrating effect of the applied mechanical stimulus, which is useful

for investigating age-related to cortical bone trabeculation. In this work, the biological and mechanical parameters are a fixed parameter introduced for each case of simulations, in order to reduce model complexity. Furthermore, such parameters must be time dependent variable, so this will be discussed in the future. Furthermore, we attempt to provide an experimental basis, which links the biological and the mechanical behavior as a function of time, to introduce it into a finite element method.

ACKNOWLEDGMENT

This work was supported by the Partenariat Hubert Curien Franco-Moroccan TOUBKAL (PHC Toubkal) Ref: 43681QG.

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